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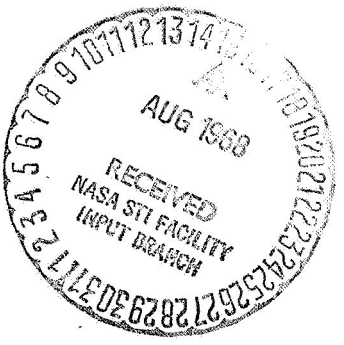

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OVERMATURITY OF THE EGG AS TERATOGENETIC FACTOR

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ABSTRACT: All manifestations due to overmaturity are due to chemical changes in the ageing egg. The author has investigated the attendant malformations in the three series of experiments.

The well-known experiments of Tornier, Braus, Spemann and others have /91* helped in elucidating the genesis of malformations to the extent that we now know that multiformation may be caused by duplication or additional multiplication of organisational centers and embryonic primordia. In the experiment, such malformations are produced either by the induced cleaving of individual centers or by transplanting of foreign centers. To date we know, however, very little about the factors causing spontaneous multiplication of primordia. Stockard in a number of papers has described how irregularities in gastrulation may be produced at the blastula stage by oxygen deficiency; these irregularities, in turn, led to various permanent disturbances and in particular to the appearance of double formation structures. Very similar results were obtained by Werber following experimental poisoning of germ tissue, and this in particular when he used acetone. Both these authors believe therefore that the occasional multiformation is primarily caused by changes in the chemical nature of the environment in which the germ is developing.

In the course of culture experiments with frogs, I have now discovered an additional teratogenetic factor, which appears to be of general significance. In /92 the course of my first experiments in this field sometime ago at the Institute of Zoology of Munich University, I obtained in a "heat" series five froglets exhibiting one to three supernumerary forelegs. At the time of metamorphosis, this series consisted of only 20 animals, and the high percentage of polymelia observed was all the more remarkable because no corresponding malformations were found among the 500 siblings grown at a lower temperature.

The obvious conclusion that the temperature factor alone was responsible for this malformation was shown to be wrong since no polymelic froglets were found among the heat-grown animals derived from normally matured animals (eggs). Overmaturity of the egg probably was of teratogenetic significance in addition to the temperature factor. In order to elucidate this matter, I repeated the experiment in the course of which I, however, increased overmaturity of the eggs and cultured the larvae in two parallel series viz. one at normal and the other one at very low temperatures.

*Numbers in the margin indicate pagination in the foreign text.

To begin with I may mention that polymelic froglets were once again obtained although not in the expected high numbers. ("Heat," i.e., a temperature of 27°C, thus, appears to represent a rather effective auxiliary agent in this respect.) The temperature once again was of a certain significance since a total of 60 malformed embryos (20%) was found in the normal series, but only approximately 5% in the cold series. Mortality also was much less in the latter series.

I was able to follow the genesis of polymelia through biogenetic development, and I found separate forelimb buds at very early stages. Whether these, however, were derived from an originally homogenous anlage or whether they developed separately is as yet not clear.

I was greatly surprised to find a very great number of animals exhibiting an axial double formation when I first examined them after hatching from the gelatine sack: in some animals I found complete katadidymus and in others frequently non-symmetric monstrosities. In addition I found numerous more or less severe pathological malformations as well as a number of completely amorphous embryos.

(Photographs and sections exhibiting these malformations were demonstrated during the meeting; a more extensive description will be given in a subsequent paper containing figures.)

Since the work done by Spemann's school on determinant processes in the /93
amphibian germ has helped to elucidate a number of pertinent questions in this field, one may assume that the teratogenetic determination of axial malformation occurs during the early stages of development and not later than during gastrulation. In the case of an amorphous malformation characterized by tissue degeneration this moment probably arrives even earlier.

A third series of experiments was undertaken by me for the elucidation of this question. Deviations occurring during segmentation and gastrulation are of significance for the group mentioned first. In normally matured eggs, four abortive micromeres are separated at the third cleavage stage, which, on polar viewing, may mask the macromere to a large extent. In overmature sibling eggs, these micromeres are without exception very much smaller. Frequently second cleavage already is an equatorial one, in which case only two micromeres are formed. These deviations from the normal process, which indicate a certain overmaturity of the egg, are significant. They, however, do not exert a direct teratogenetic affect, a fact demonstrated by analogous observations in centrifuged and packed eggs. The morula of overmature eggs is characterized furthermore by the frequent finding of not properly touching cell surfaces. This latter finding reminds the viewer of the picture of "spontaneous blastotomy" (Bataillon). Once one however recalls how easily normal germs fuse on direct contact, then one may at first regard these cleavage products as the expression of a loosening of both the general continuity and the interactions of germinal cells. These disturbances of coordination are particularly severe when individual regions develop at different rates or when devitalised tissue is interspersed between normally developing tissue. The finding last mentioned represents a specific indication for local irregularities due to overmaturity of the egg. Since overmaturity—representing a preliminary step toward the death of the egg—denotes a decreased vitality, it follows that the surface of the blastula (of such eggs) contains regions weakened to various degrees. These differences in vitality are frequently large

ones, and individual, viable parts may proceed with development by autodifferentiation. This form of differentiation may be observed first during the formation of the blastopore, which formation frequently commences simultaneously at a number of sites; this, however, normally occurs in a way that the primary folds all are at approximately the same level. After individual observation of such double gastrulae, I have obtained embryos exhibiting spina bifida (in a number of cases, however, corrective regulation led to the development of normal larvae). That I was unable to observe the development of the highly interesting symmetrical dicephalous monstrosities is, of course, due to the fact that they represent /94
relatively rare occurrences. In accordance with Stockard, I assume, however, that the occurrence of a secondary blastopore invagination represents the decisive step in the development of this particular form of monstrosity.

It is obvious that all manifestations due to overmaturity are due to chemical changes in the ageing egg. Although the processes in question are of an endogenous nature, one cannot exclude the possibility that the results obtained in my experiments with overmature eggs and those obtained by Stockard and by Werber with the aid of chemical agents may be viewed against a commom background.

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